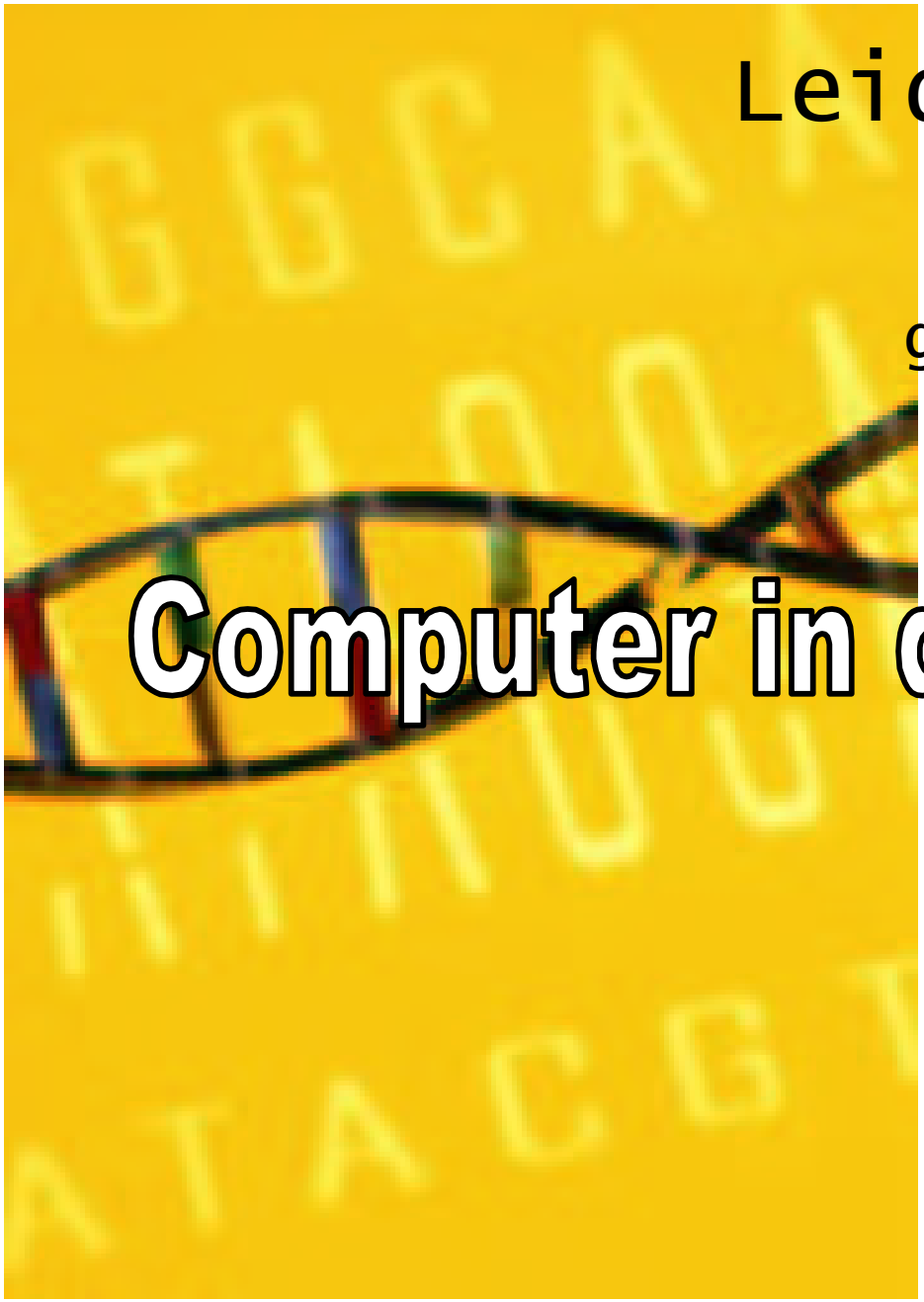


Leidsch β-congresch

grenzen in de wetenschap

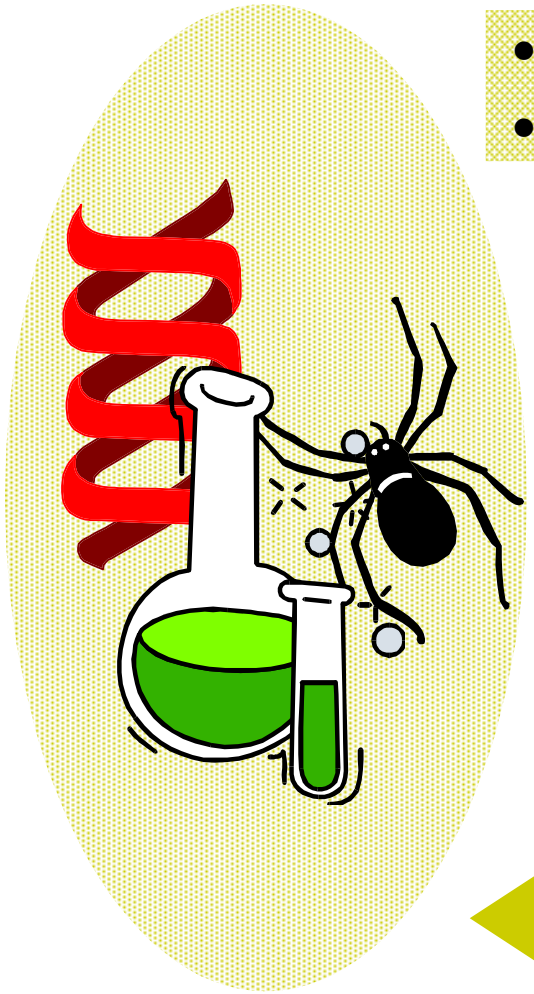
Computer in de Reageerbuis

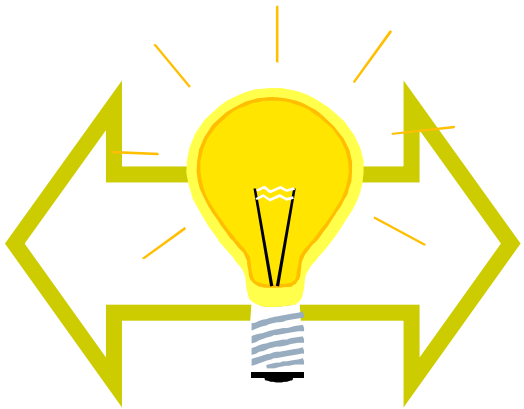
DNA computing

Hendrik Jan Hoogeboom
informatica (LIACS)

natural computation

- genetische algoritmen
- neurale netwerken





DNA computing

Physicists plunder life's tool chest

If we look inside the cell, we see extraordinary machines that we couldn't make ourselves, says Len Adleman. "It's a great tool chest - and we want to see what can we build with it."

Adleman created the first computer to use DNA to solve a problem. He was struck by the parallels between DNA, with its long ribbon of information, and the theoretical computer known as the Turing Machine.

Nature News Service april 2003

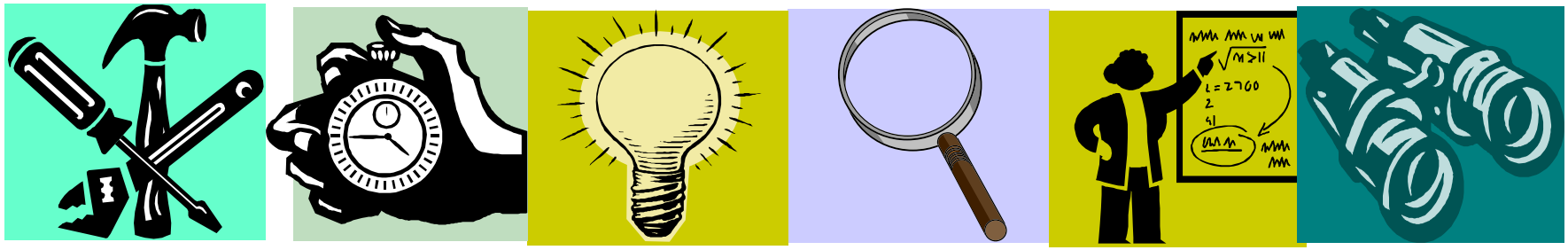
Physicists plunder life's tool chest

Adleman tackled the famous 'travelling salesman' problem - finding the shortest route between cities. Such problems rapidly become mind-boggling. The only way is to examine every possible option. With many cities, this number is astronomical.

DNA excels at getting an astronomical amount of data into a tiny space. "One gram of DNA can store as much information as a trillion compact discs," says Adleman. Myriad DNA molecules can examine every possible route at once, rather than one at a time, as in a conventional computer.

inhoudsopgave

\ DNA … de gereedschapskist
\ complexiteit van problemen … P & NP
  Hamilton Path Problem
\ Adlemans algoritme
\ commentaar
\ theorie … Turing machine
\ recent werk + toekomstvisie



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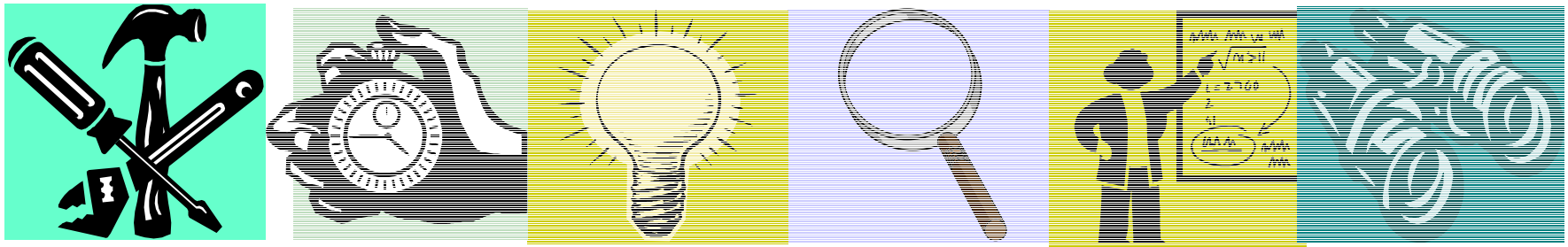
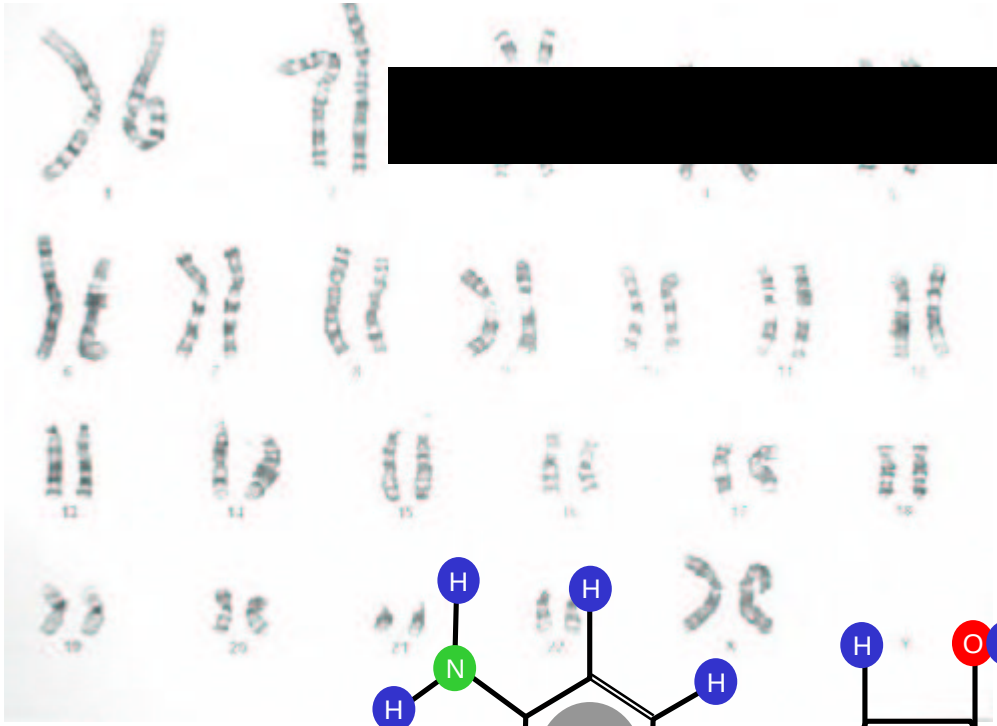
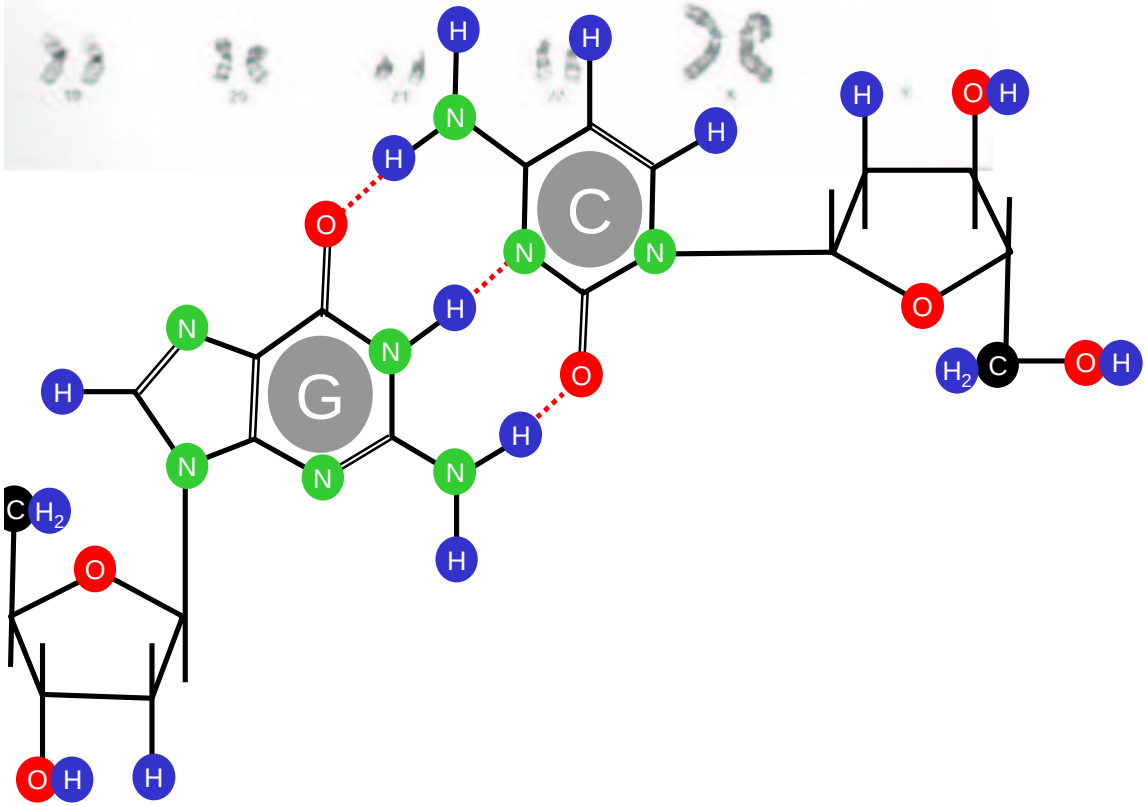
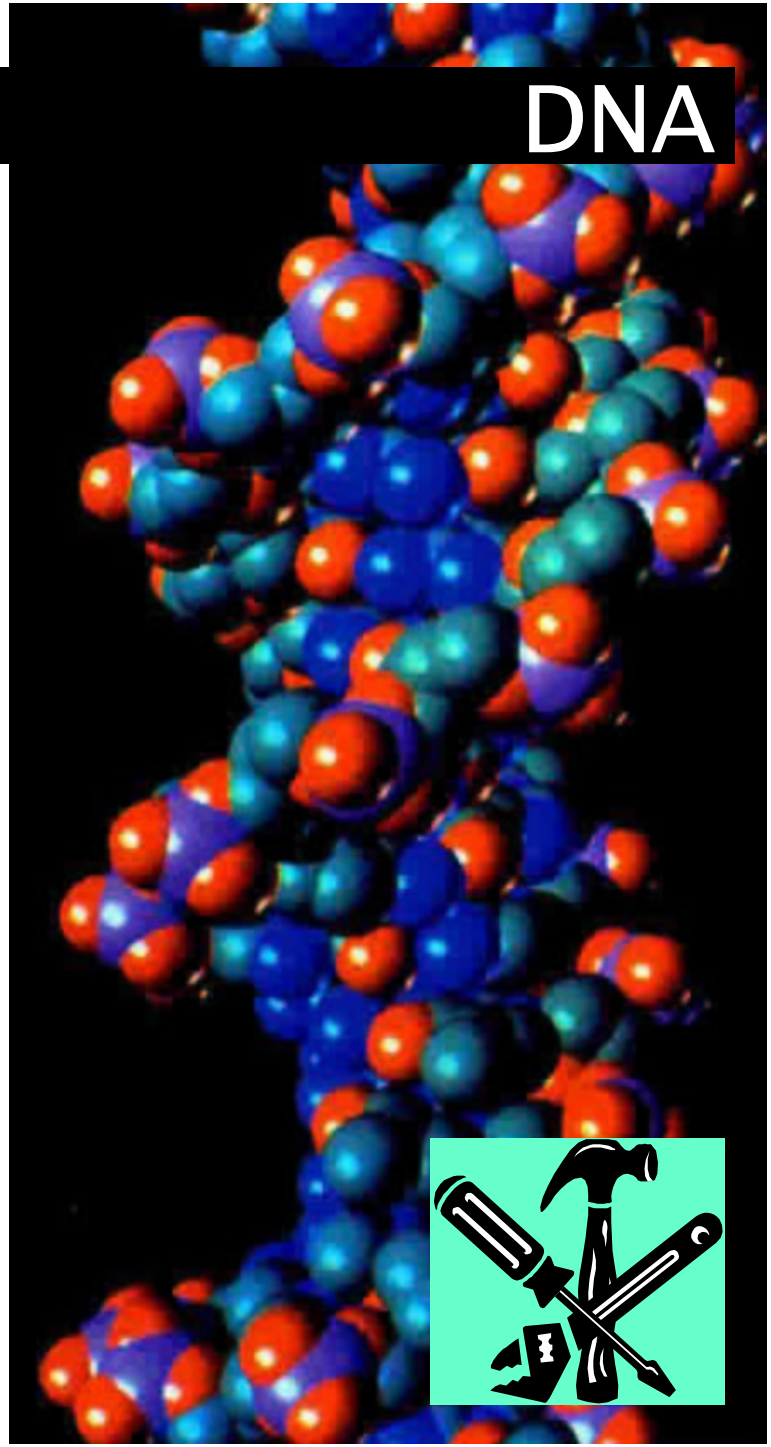
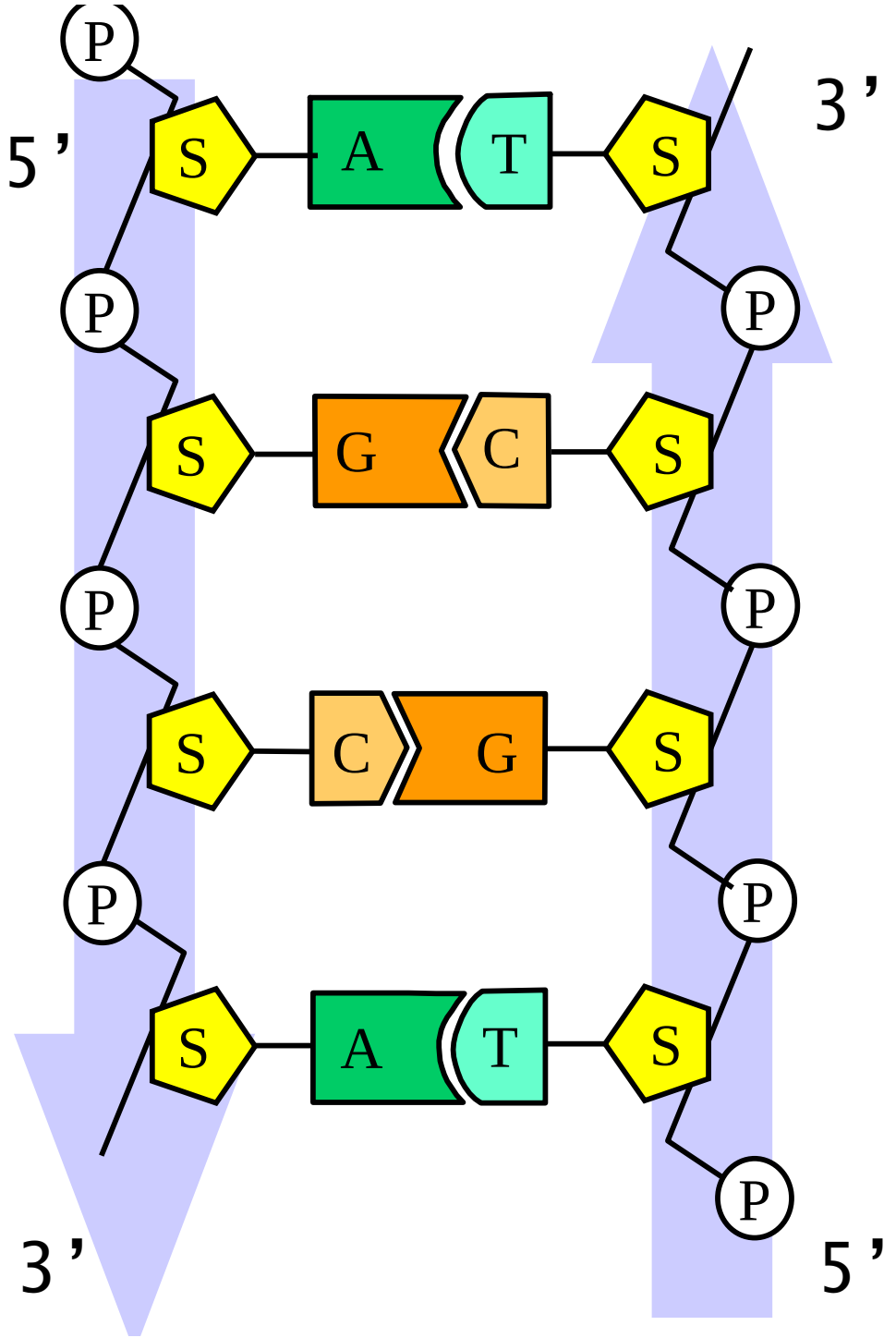


DNA







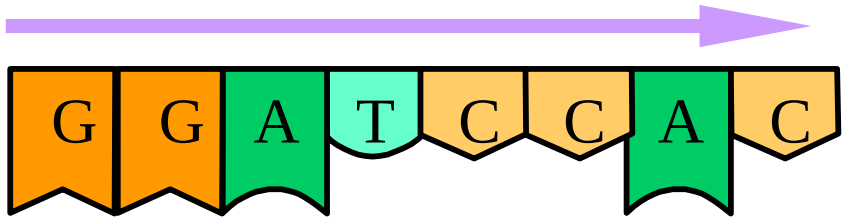


DNA

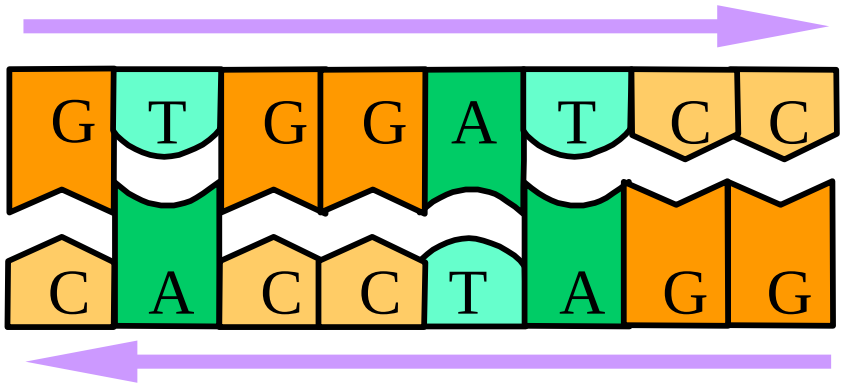
baseparen
Watson & Crick

A=T
adenine - thymine
C≡G
guanine - cytosine

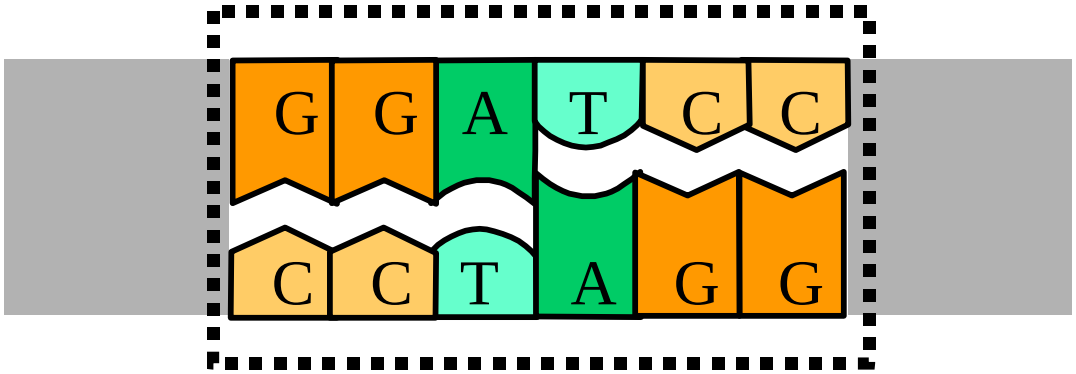
annealing & denaturing



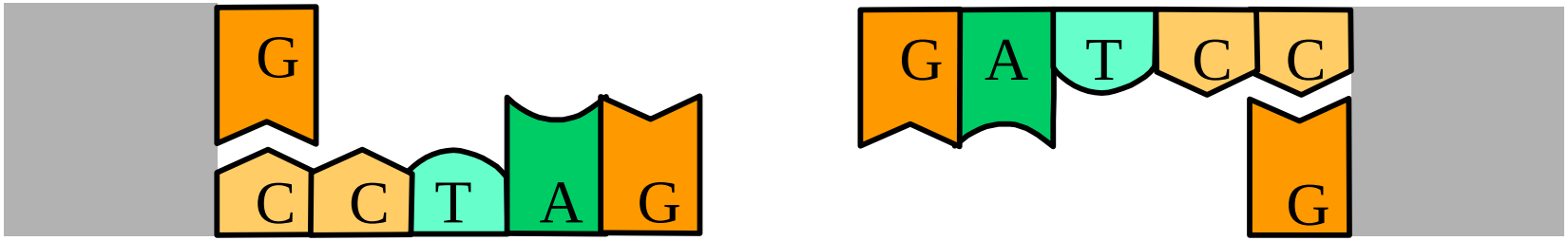
complementair



restriction enzymes

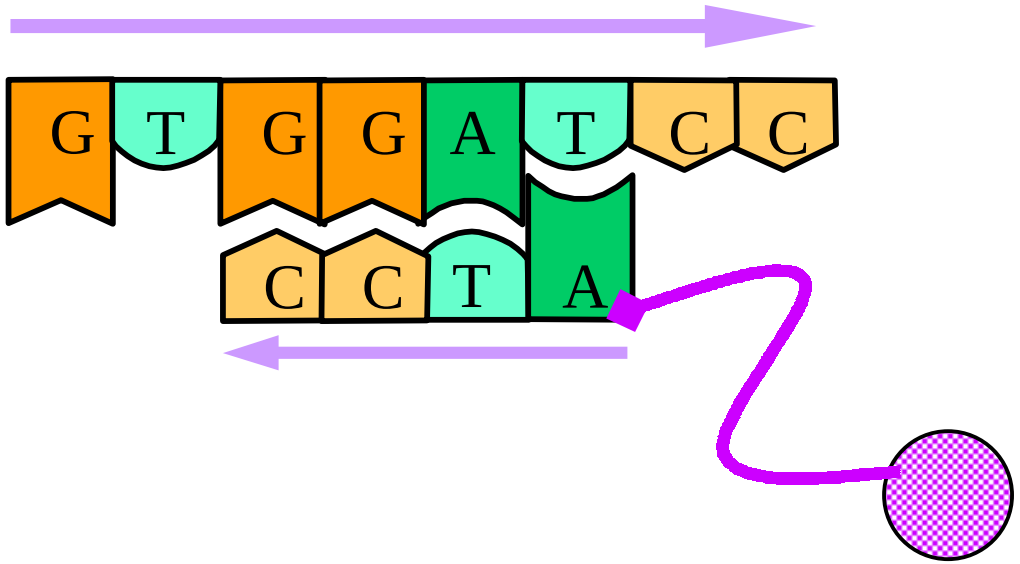


BamHI



sticky ends

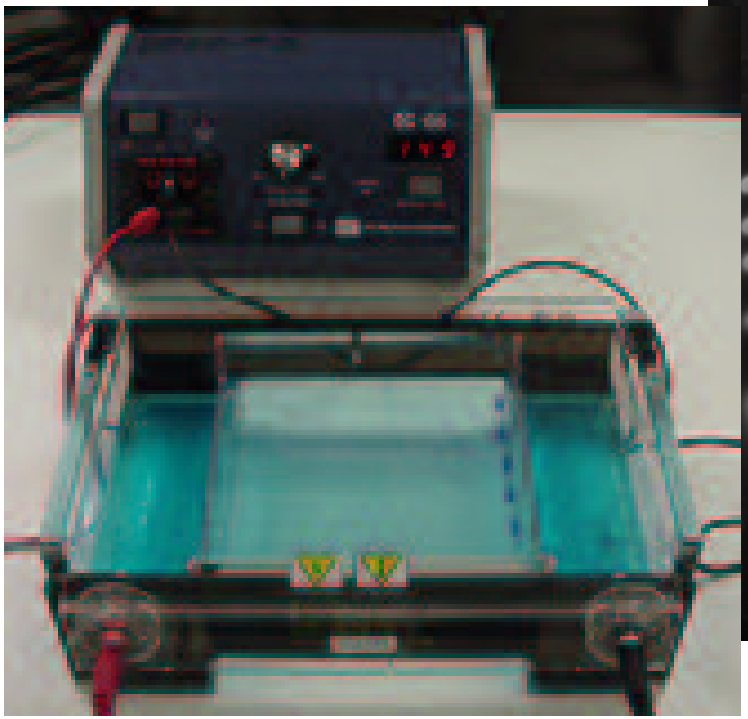
selection

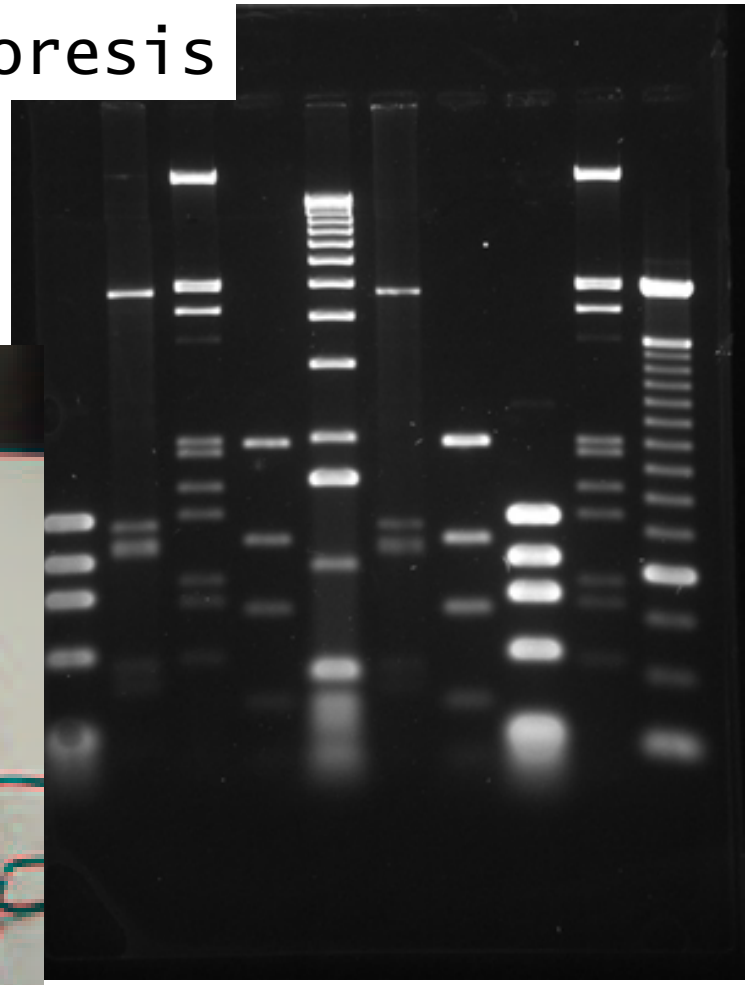


magnetic beads

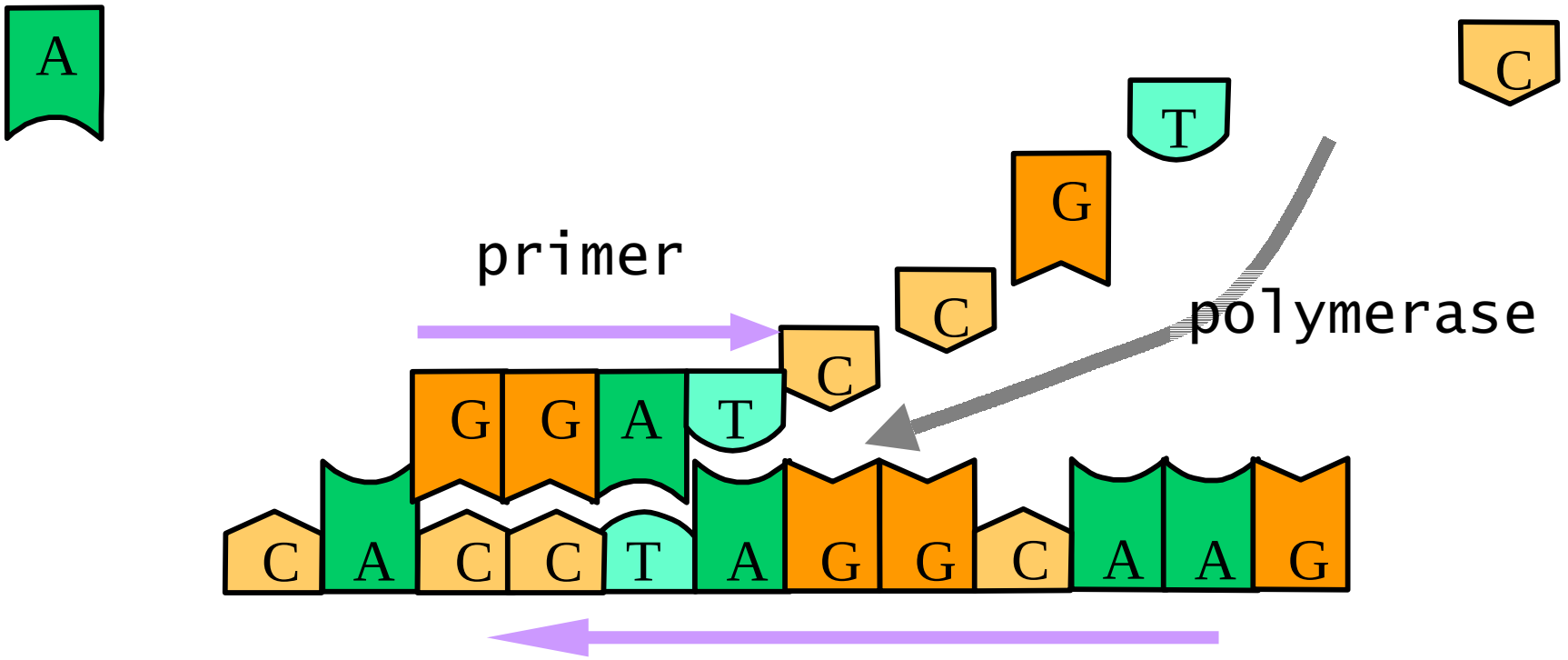
separation on length

DNA gel electrophoresis





multiplication / amplification



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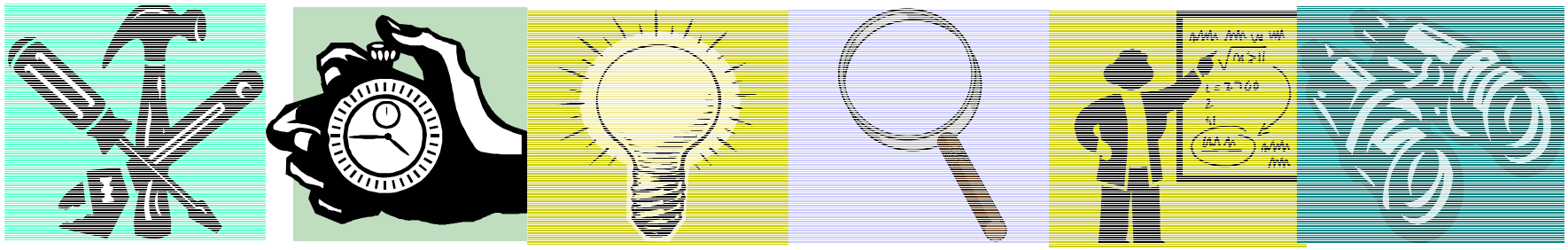


grenzen: complexiteit

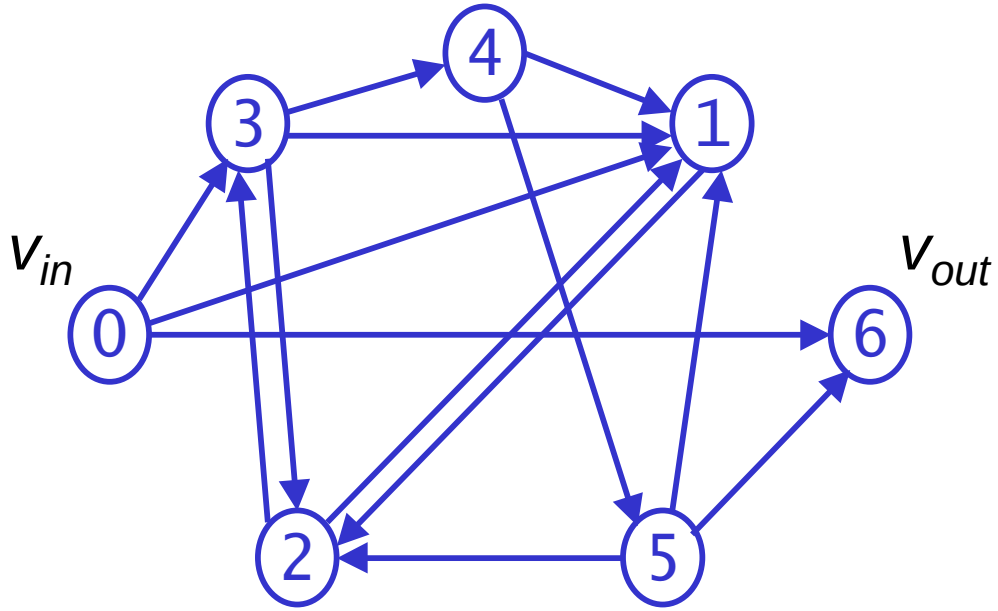
	n=10	30	50	60
n	10^{-5}s	3×10^{-5}s	5×10^{-5}s	6×10^{-5}s
n^2	10^{-4}s	9×10^{-4}s	2×10^{-3}s	4×10^{-3}s
n^5	10^{-1}s	24 s	1.7 m	13 m
2^n	10^{-3}s	18 m	13 d	366 c
3^n	6×10^{-2}s	6.5 y	3855 c	10^{13} c

second
minute
day
year
century

polynomiaal vs.
exponentieel

	nu	100x	1000x
n	N	100N	1000N
n^2	N	10N	32N
n^5	N	2.5N	4N
2^n	N	N+6.6	N+10
3^n	N	N+4.2	N+6.3

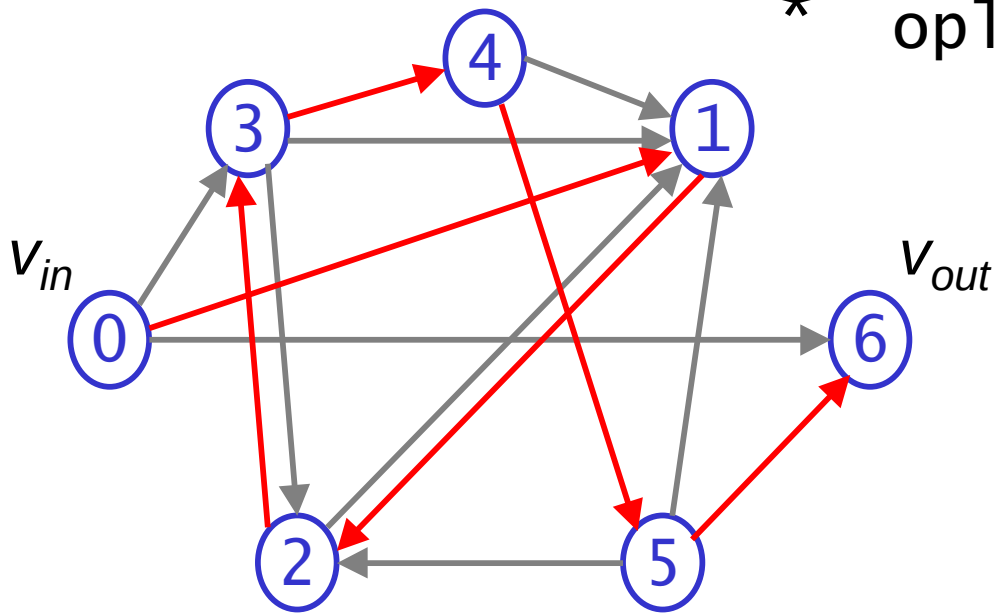
HPP: Hamilton Path Problem



'travelling salesman'

gegeven: knopen en verbindingen
vraag: bestaat er een wandeling die elke knoop precies één keer aandoet ?

HPP: Hamilton Path Problem



* oplossing

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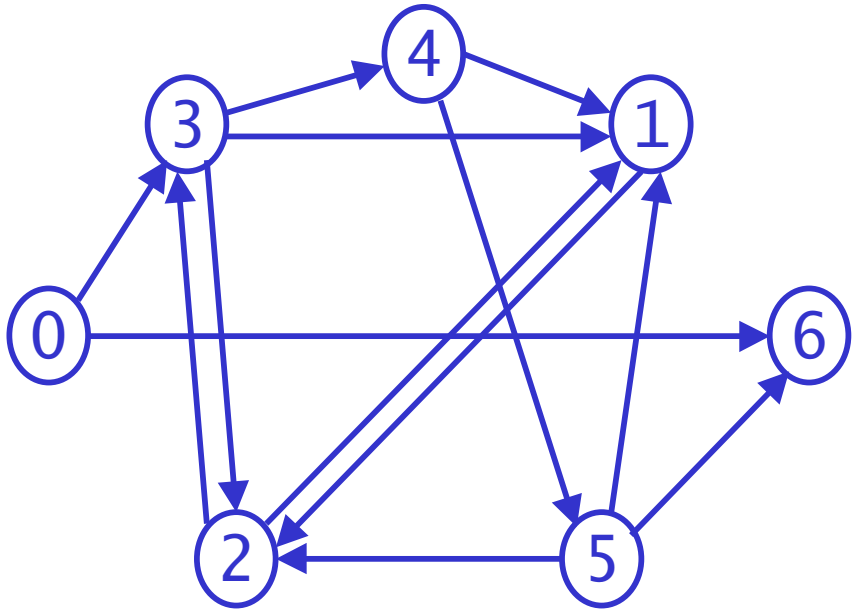

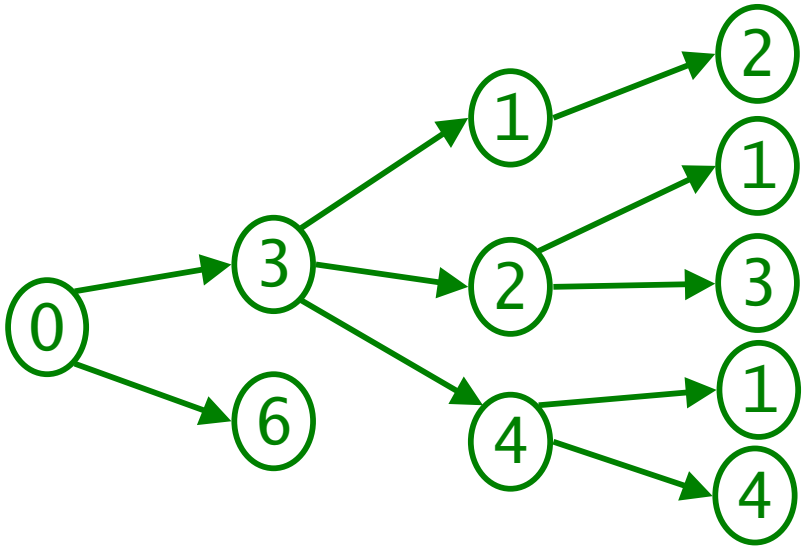

* geen oplossing?

exponentiële tijd:
alle mogelijkheden proberen

representatief:
'NP compleet'

heuristieken

grenzen (theorie) - P vs. NP

P

polynomiaal algoritme
om oplossing te bepalen

NP

polynomiaal algoritme
om oplossing te verifiëren

NP-compleet

millenium prize problem P=NP
www.claymath.org/Millennium_Prize_Problems/

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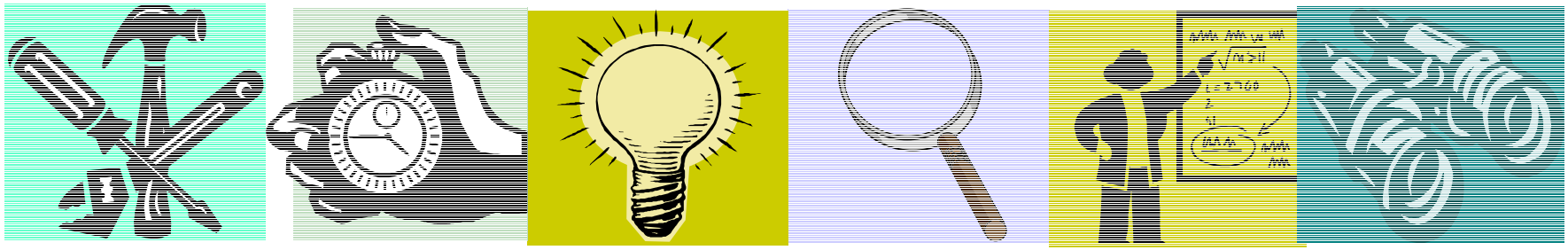
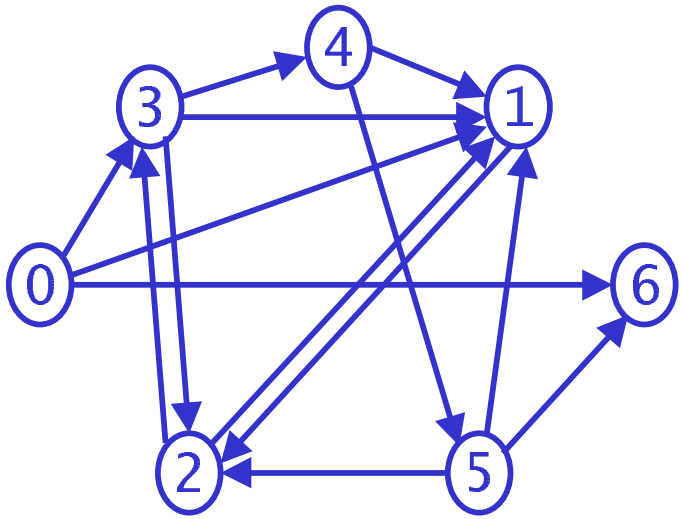


Adleman's algorithm

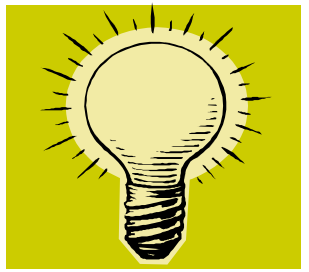


1. generate 'all' paths

   keep only paths
2. … from v_{in} to v_{out}
3. … that enter n vertices
4. … that enter all vertices

5. if any path remains OK

máár
… in DNA
… alle paden parallel
'*massive parallellism*'



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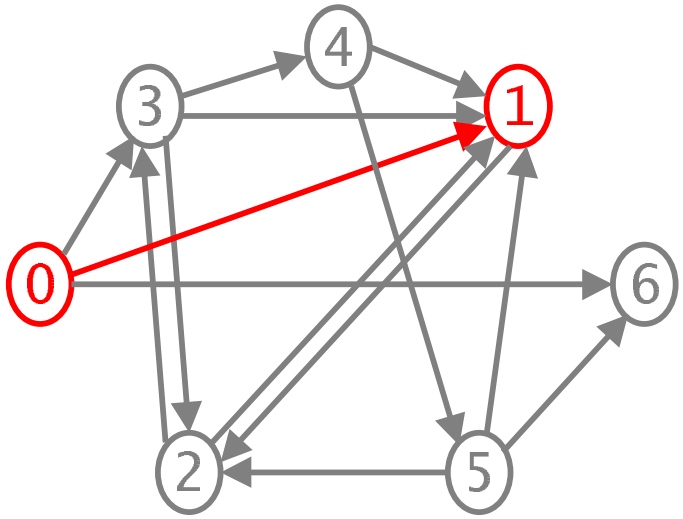

0. coding the graph
1. generate 'all' paths

   keep only paths
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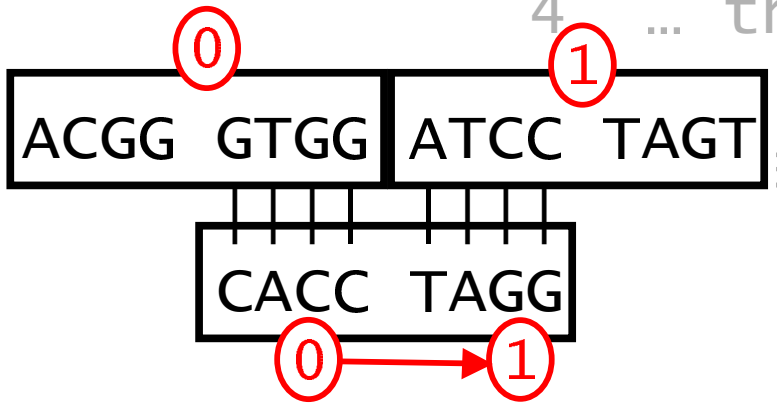
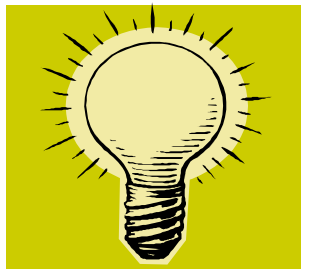
   any path remains OK





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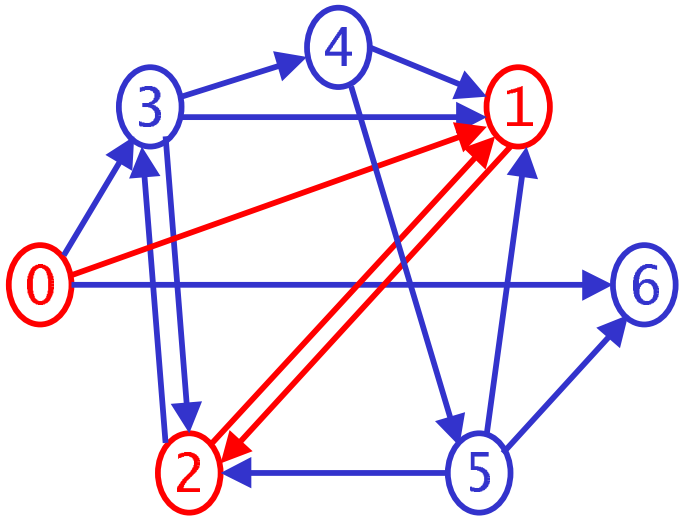

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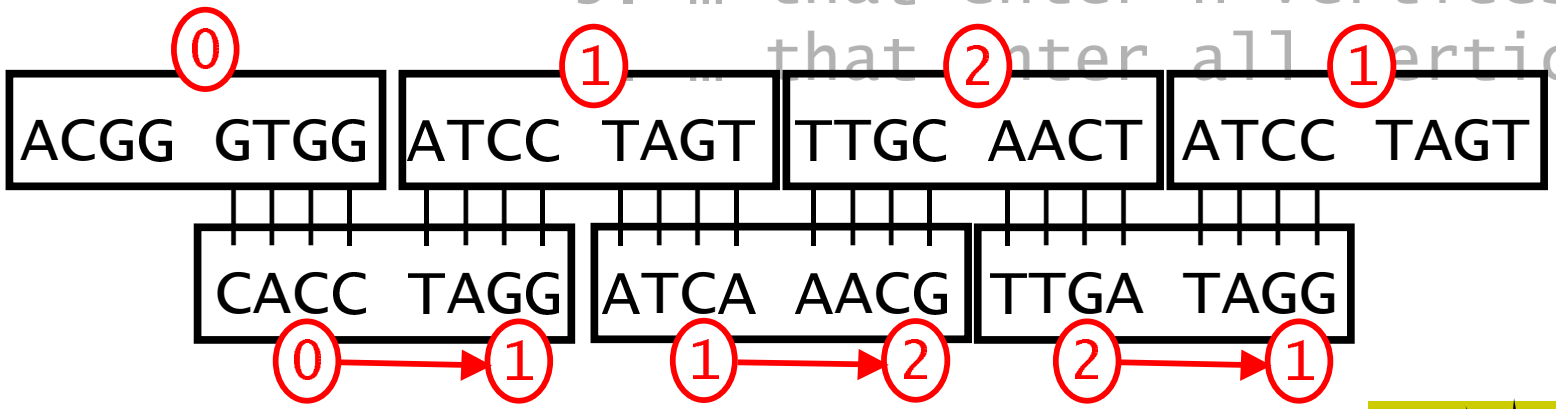

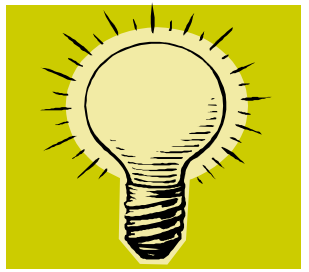

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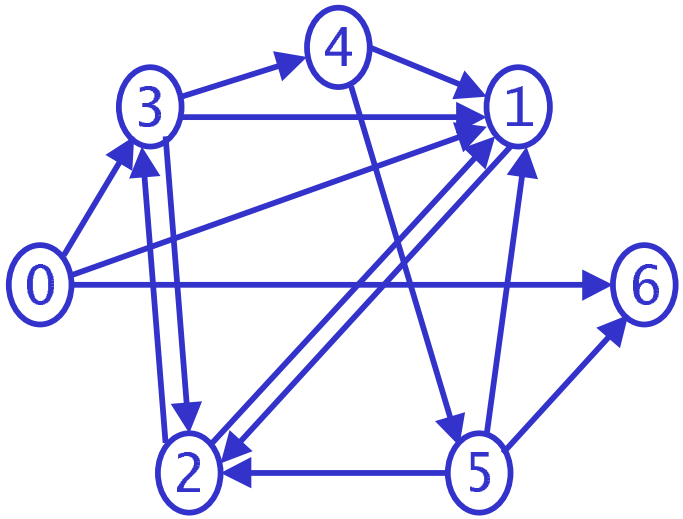

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- PCR with v_{in} and v_{out} primers
- gel: separate on length, amplify & purify
- magnetic beads: select strands
- PCR amplification & gel

inhoudsopgave

\ DNA … de gereedschapskist
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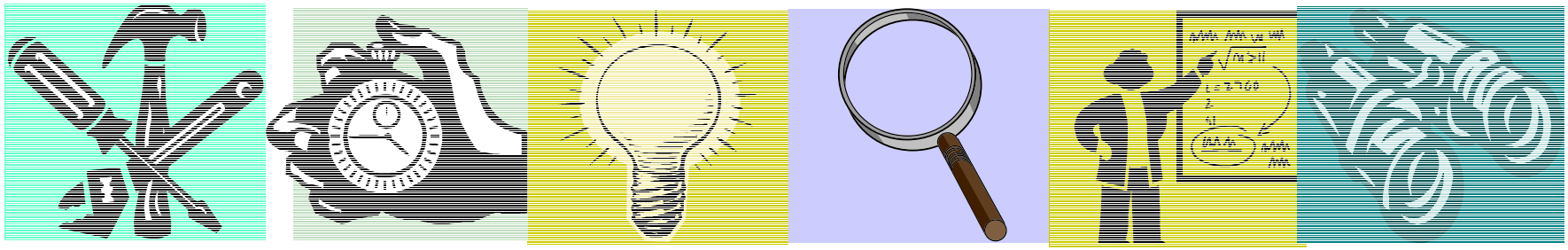
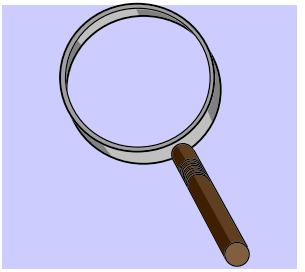


comments …

- "clear that the methods could be scaled up to … larger graphs"
  - + bath tub of DNA ?
  - + suitable algorithms
- approximately 7 days of lab work
  - + automation
  - + alternative molecular algorithms
- possibility of errors
  - + pseudopaths: accidental ligation
  - + PCR, separation procedures
  - + hairpin loops
  - + stability when scaled



comments …

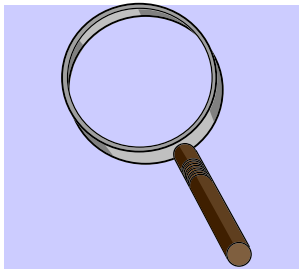
- “power of this method of computation”
  - 10^{14} operations 10^{20} plausable
  - exceed supercomputers by thousandfold

:)

- “not clear whether … used to solve real computational problems”

. multiplying 100 digit numbers

- potential: massively parallel searches



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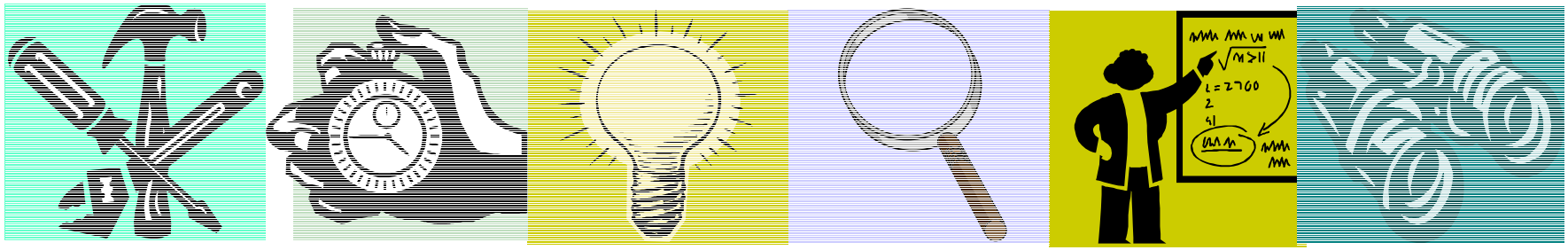
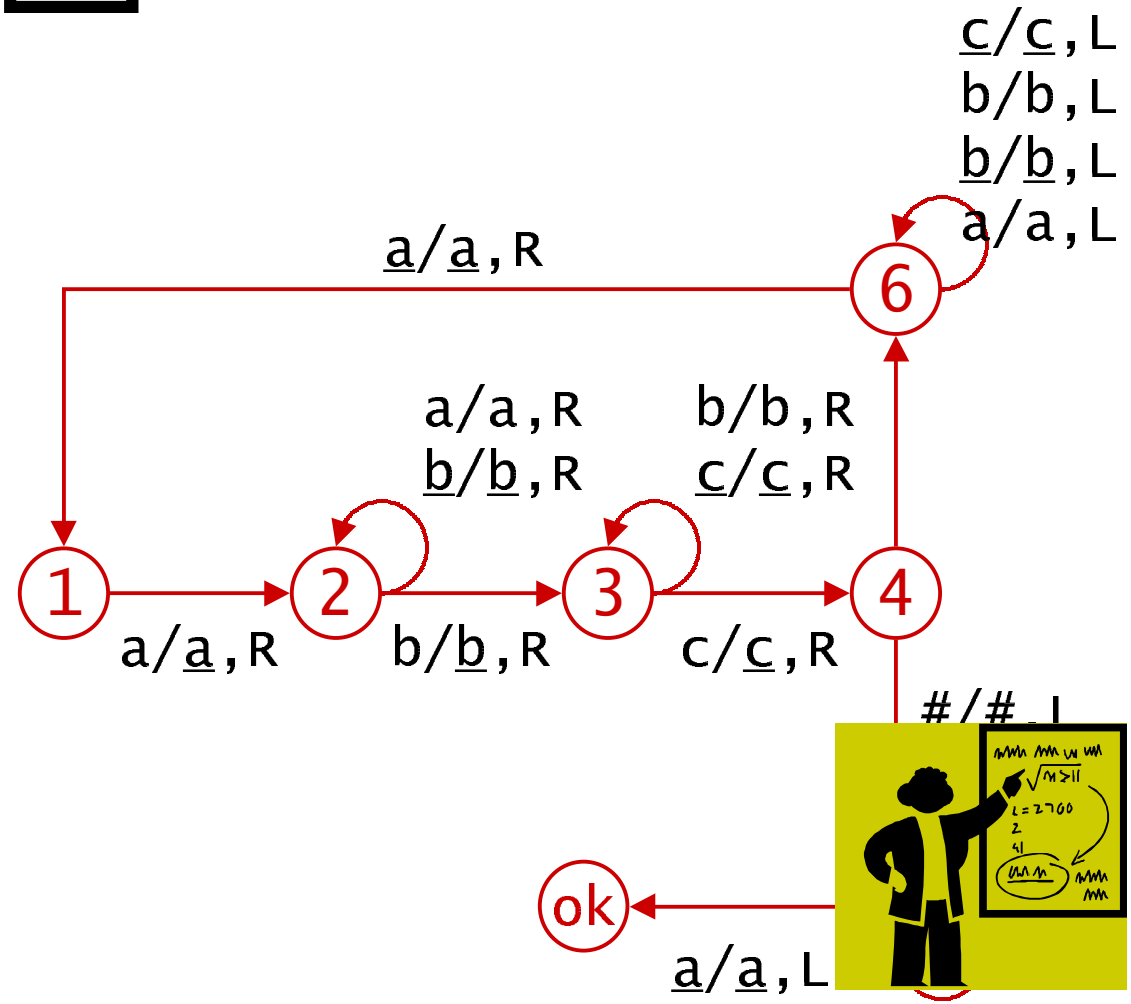


Turing machine

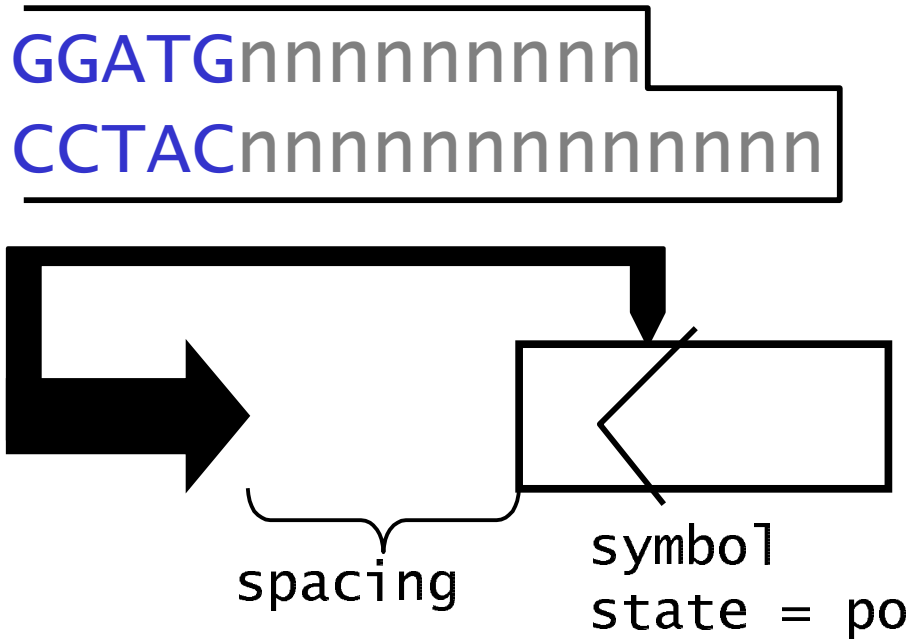
#	a	a	a	a	a	b	b	b	b	b	c	c	c	c	c	#

tape

1. mark a
2. move to b's
   mark b
3. move to c's
   mark c
4. if another c
5. then back to a's
   goto 1.
   else back to a's
6. check marks
   stop

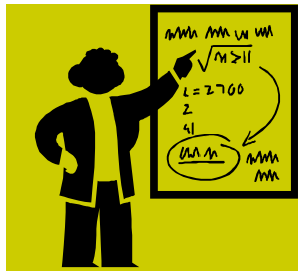


‘universal’ Turing machine



Rothemund
*Fok*I
circular DNA

- cut states with restriction enzyme
- mix ‘instructions’ with ‘tape’
- ‘activate’ instructions (cut protected end)
- ligate to form circles
- cut old symbol
- recircularize



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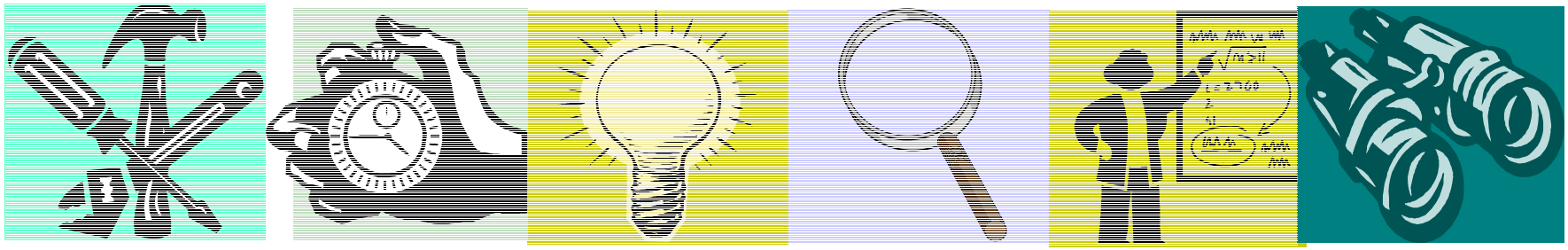
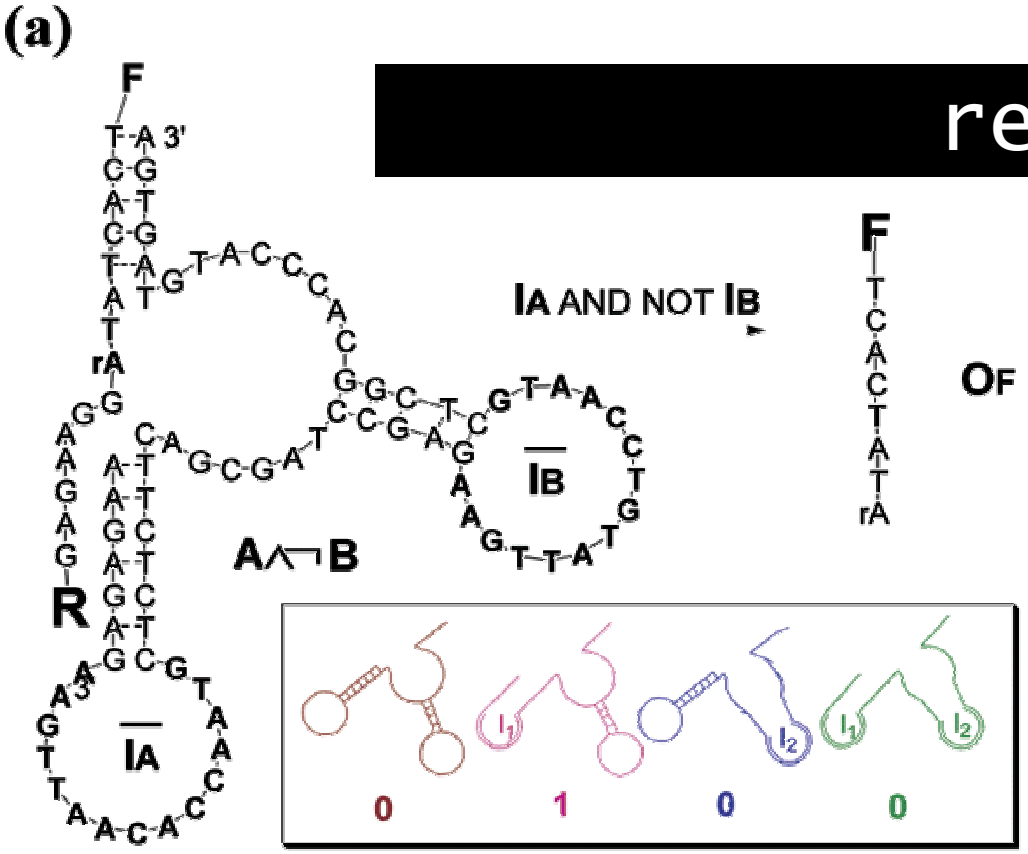
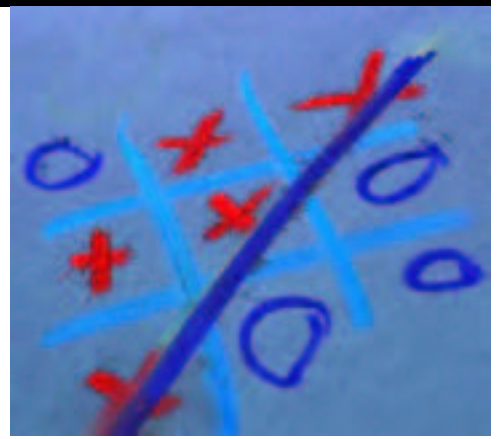
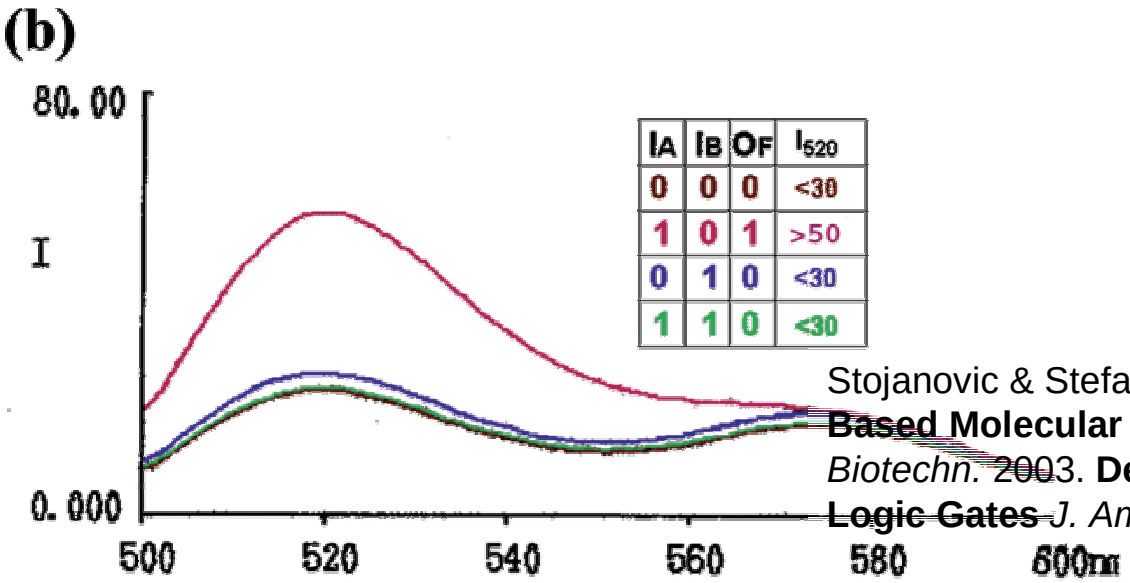


recently in Nature



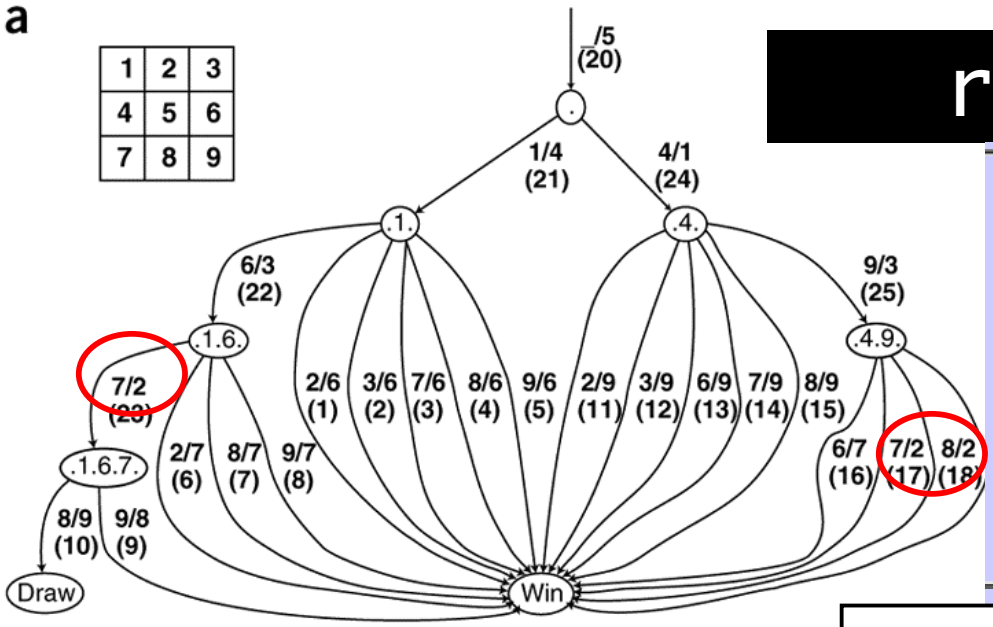


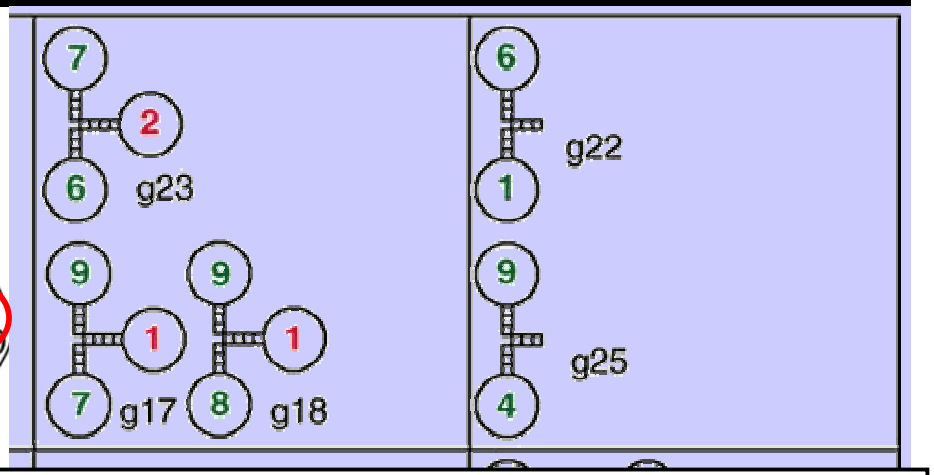


logische schakeling fluoricentie

Stojanovic & Stefanovic, **Deoxyribozyme-Based Molecular Automaton**. *Nature Biotechn.* 2003. **Deoxyribozyme-Based Logic Gates** *J. Am. Chem. Soc*. 2002

recently in Nature





$$o_2 = (i_6 \wedge i_7 \wedge \neg i_2) \vee (i_7 \wedge i_9 \wedge \neg i_1) \vee (i_8 \wedge i_9 \wedge \neg i_1)$$

b

$$o_1 = \underbrace{i_4}_{\text{edge (24)}}$$

$$o_2 = \underbrace{(i_6 \wedge i_7 \wedge \neg i_2)}_{\text{edge (23)}} \vee \underbrace{(i_7 \wedge i_9 \wedge \neg i_1)}_{\text{edge (17)}} \vee \underbrace{(i_8 \wedge i_9 \wedge \neg i_1)}_{\text{edge (18)}}$$

$$o_3 = \underbrace{(i_1 \wedge i_6)}_{\text{edge (22)}} \vee \underbrace{(i_4 \wedge i_9)}_{\text{edge (25)}}$$

$$o_4 = \underbrace{i_1}_{\text{edge (21)}}$$

$$o_5 = \underbrace{1}_{\text{edge (20)}}$$

$$o_6 = \underbrace{(i_1 \wedge i_2 \wedge \neg i_6)}_{\text{edge (1)}} \vee \underbrace{(i_1 \wedge i_3 \wedge \neg i_6)}_{\text{edge (2)}} \vee \underbrace{(i_1 \wedge i_7 \wedge \neg i_6)}_{\text{edge (3)}} \vee \underbrace{(i_1 \wedge i_8 \wedge \neg i_6)}_{\text{edge (4)}} \vee (\ldots$$

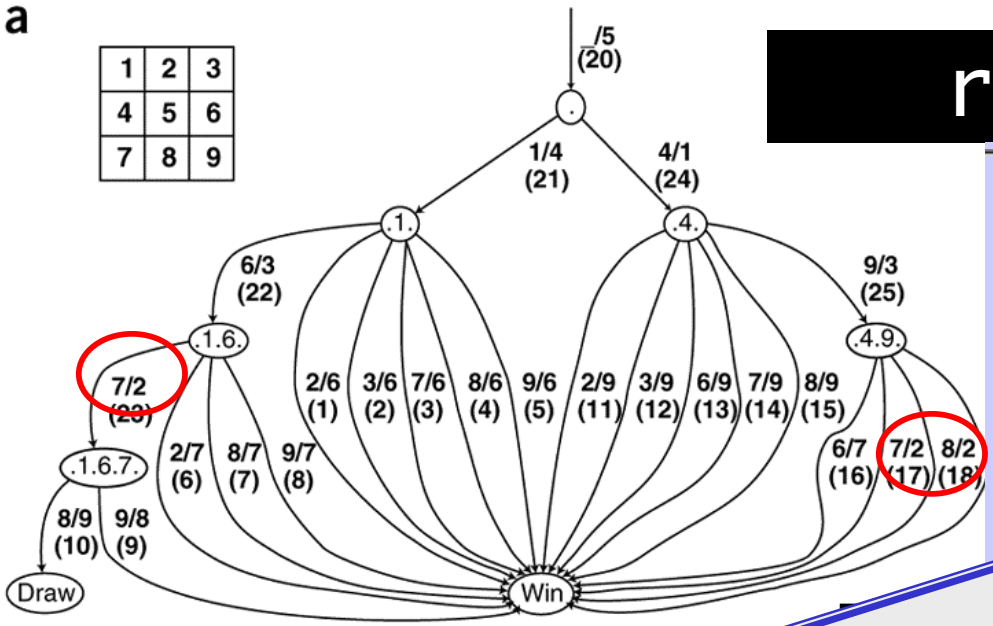
$$o_7 = \underbrace{(i_2 \wedge i_6 \wedge \neg i_7)}_{\text{edge (6)}} \vee \underbrace{(i_6 \wedge i_8 \wedge \neg i_7)}_{\text{edge (7)}} \vee \underbrace{(i_6 \wedge i_9 \wedge \neg i_7)}_{\text{edges (8) and (16)}} \vee \underbrace{(i_9 \wedge i_2 \wedge \neg i_1)}_{\text{edge (19)}}$$

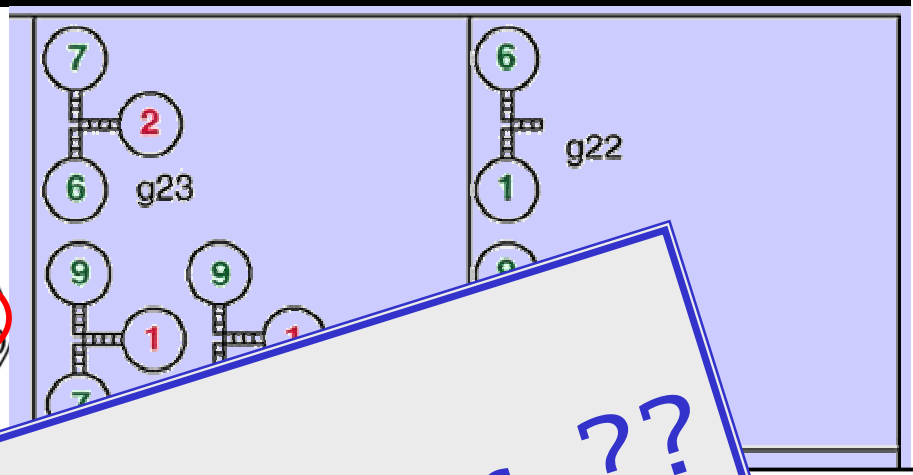
$$o_8 = \underbrace{i_9 \wedge i_7 \wedge \neg i_4}_{\text{edge (9)}}$$

$$o_9 = \underbrace{(i_7 \wedge i_8 \wedge \neg i_4)}_{\text{edge (10)}} \vee \underbrace{(i_4 \wedge i_2 \wedge \neg i_9)}_{\text{edge (11)}} \vee \underbrace{(i_4 \wedge i_3 \wedge \neg i_9)}_{\text{edge (12)}} \vee \underbrace{(i_4 \wedge i_6 \wedge \neg i_9)}_{\text{edge (13)}} \vee (\ldots$$

i_1 TCT GCG TCT ATA AAT
i_2 ATC GTA TGT TGT TCA
i_3 GTA TAG TCT GTT TGT
i_4 G TAA GTG CTC AAA TGT C
i_5 G TCT AAT TCT CAC GGT C

recently in Nature





maar …
is dit een computer ??

b

$$o_1 = \underbrace{i_4}_{\text{edge (24)}}$$

$$o_2 = \underbrace{(i_6 \wedge i_7 \wedge \neg i_2)}_{\text{edge (23)}} \vee$$

$$o_3 = \underbrace{(i_1 \wedge i_6)}_{\text{edge (22)}} \vee \underbrace{(i_4 \wedge i_9)}_{\text{edge (25)}}$$

$$o_4 = \underbrace{i_1}_{\text{edge (21)}}$$

$$o_5 = \underbrace{1}_{\text{edge (20)}}$$

$$o_6 = \underbrace{(i_1 \wedge i_2 \wedge \neg i_6)}_{\text{edge (1)}} \vee \underbrace{(i_1 \wedge i_3 \wedge \neg i_6)}_{\text{edge (2)}} \vee \underbrace{(i_1 \wedge i_7 \wedge \neg i_6)}_{\text{edge (3)}} \vee \underbrace{(i_1 \wedge i_8 \wedge \neg i_6)}_{\text{edge (4)}} \vee$$

$$o_7 = \underbrace{(i_2 \wedge i_6 \wedge \neg i_7)}_{\text{edge (6)}} \vee \underbrace{(i_6 \wedge i_8 \wedge \neg i_7)}_{\text{edge (7)}} \vee \underbrace{(i_6 \wedge i_9 \wedge \neg i_7)}_{\text{edges (8) and (16)}} \vee \underbrace{(i_9 \wedge i_2 \wedge \neg i_1)}_{\text{edge (19)}}$$

$$o_8 = \underbrace{i_9 \wedge i_7 \wedge \neg i_4}_{\text{edge (9)}}$$

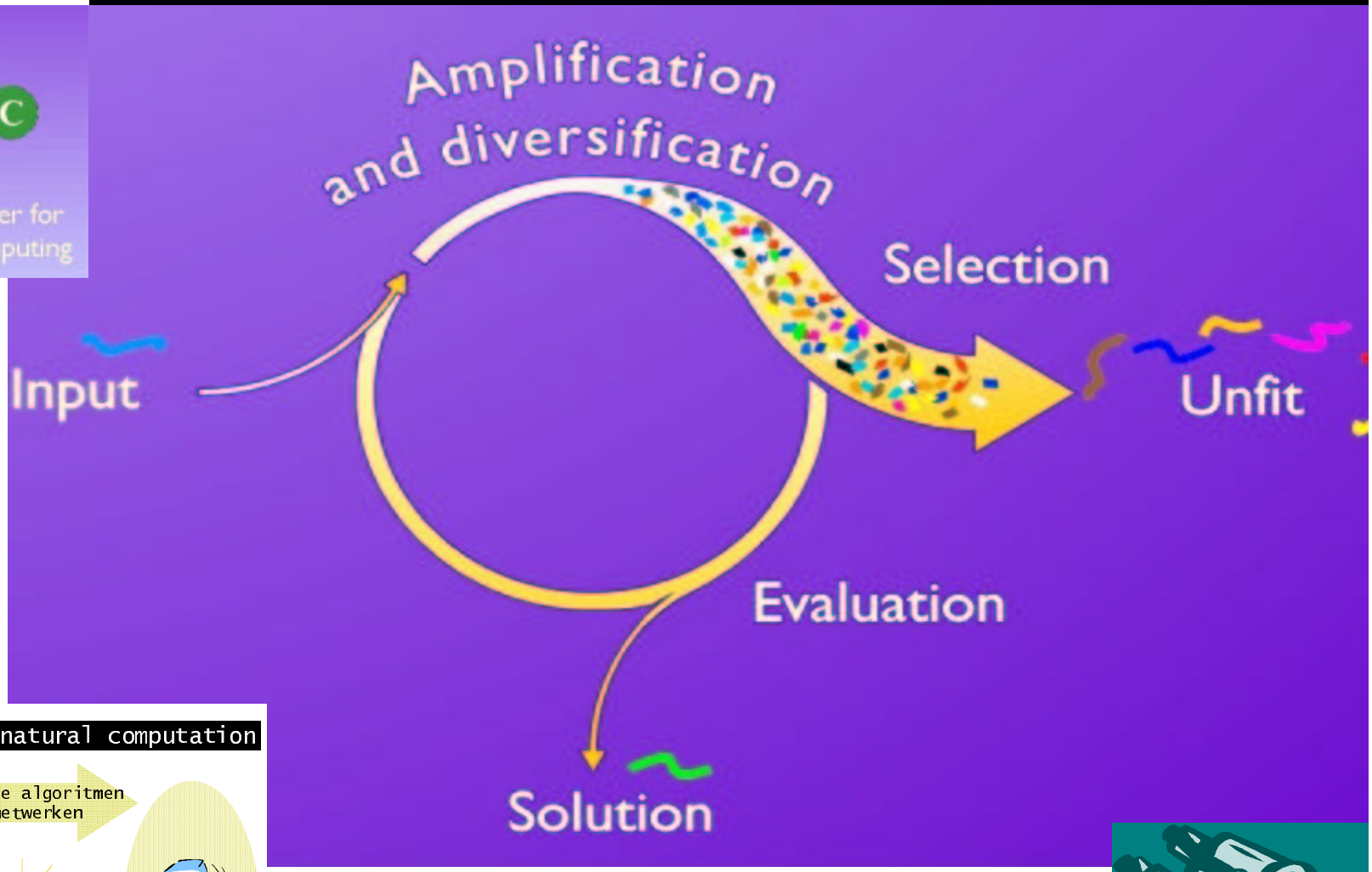
$$o_9 = \underbrace{(i_7 \wedge i_8 \wedge \neg i_4)}_{\text{edge (10)}} \vee \underbrace{(i_4 \wedge i_2 \wedge \neg i_9)}_{\text{edge (11)}} \vee \underbrace{(i_4 \wedge i_3 \wedge \neg i_9)}_{\text{edge (12)}} \vee \underbrace{(i_4 \wedge i_6 \wedge \neg i_9)}_{\text{edge (13)}} \vee$$

$$\neg i_1) \vee (i_8 \wedge i_9 \wedge \neg i_1)$$

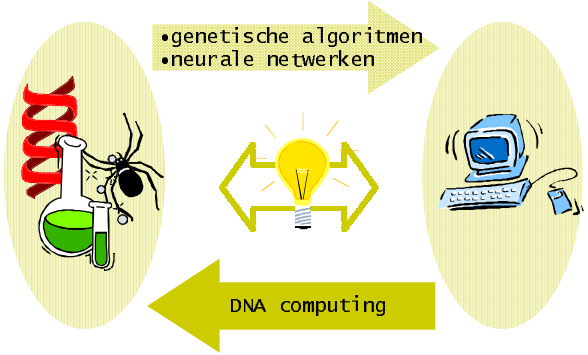
i_1 TCT GCG TCT ATA AAT
i_2 ATC GTA TGT TGT TCA
i_3 GTA TAG TCT GTT TGT
i_4 G TAA GTG CTC AAA TGT C
i_5 G TCT AAT TCT CAC GGT C

evolutionary DNA computing

Leiden Center for Natural Computing



natural computation



grenzen (praktijk)

There are many practical hurdles. Even with the best techniques of today, DNA still lags behind silicon computers," says Ehud Shapiro. Instead, he advocates creating DNA devices that can do things, and go to places, that silicon can't - such as inside our cells, to make and control drugs.

...

Ultimately, Seeman hopes to build DNA scaffolding for electrical circuits, or for other molecular machines.

...

Yurke is focusing on DNA machines with moving parts. In 2000, he and his colleagues devised a set of DNA tweezers ....

Nature News Service april 2003

klaar …